REMARKS

The Office Action

Claims 12-15 and 22-35 were pending in this matter. With this reply, claims 13, 26, and 27 have been cancelled and claims 24 and 34-37 have been withdrawn. Claims 1-11 and 16-21 were previously cancelled. Thus, with this reply, claims 12, 14, 15, 22-25, and 28-33 are pending and under examination. Claims 12-15, 22, 23, 25, and 28-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claims 12, 13, 15, 22, 23, and 28-32 stand rejected under 35 U.S.C. § 102(b) for lack of novelty.

Rejection under 35 U.S.C. § 112, first paragraph, for lack of written description

Claims 12-15, 22, 23, 25, and 28-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. As a basis for this rejection the Office Action at pages 7, 8 and 10 states:

> A mere statement that such compounds would be desirable for treatment of a host of diseases does not sufficiently provide ample written description pages describing the full breadth of the corticosteroids-bulky group and corticosteroids-charged group conjugates and specifically of the biological activity required to treat a host of diseases as instantly claimed. The specification does provide examples of what qualify as compounds of the claimed invention (see, e.g, disclosure, pages 29-36, Examples 3-8), however, these are limited to a few examples such as a polyguanidine peptoid derivative of prednisolone (Example 3), a hyaluronic acid conjugate of triamcinolone (Example 5), an mPEG conjugate of Budesonide (Example 6), a beclomethasone dimer (Example 7). As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations within the method are limitless to any class of bulky group or charged group conjugated with the claimed corticosteroid....
>
> ...Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide examples of methods of treating administrating conjugates of a representative number of corticosteroid conjugates encompassed by the instant claims to treat all the instantly claimed illnesses.
>
> ...Applicant's arguments are not deemed persuasive with respect to the attached bulky groups of any molecular composition having molecular weight greater than 500, 500, 700, 800, 900 or 1000 daltons. Please note there is no upper limit for the bulky groups and bulky groups that are charged. With respect to the charged groups with 2,3,4,5,6,7,8, 9, 10 or more negatively charged moieties, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more positively charged moieties, these are not adequately described within the disclosure except for

mentioning some charged moieties (carboxylate, phosphodiester, phosphoramide, borate, phosphate, phosphonate, phosphonate ester, sulfonate, sulfate, thiolate, phenolate, ammonium, amidinium, guanidium, quaternary ammonium, and imidazolium moieties) and bulky groups (poly-arginine, poly lysine, poly-aspartic acid, poly-glutamic acid or polyhistidine, hyaluronic acid. The disclosure presents working examples with guanidine and hyaluronic acid. With regards to applicant's exhibits A-D, Examiner has carefully considered them but not deemed them persuasive with respect to the instantly claimed very broad genus of 'autoimmune or inflammatory condition' which is not expressly defined in the disclosure, and encompasses any kind of autoimmune disease, such as HIV and/or any inflammatory disease including, e.g., obesity.

Applicant has addressed these rejections by amending claim 12 and with the following remarks.

The invention as claimed features a method for treating an autoimmune or inflammatory condition by administering a peripherally acting corticosteroid conjugate. The corticosteroid conjugate has three characteristic components: a corticosteroid covalently tethered, via a linker, to a group that is bulky. The function of the bulky group is solely to increase the size of the corticosteroid sufficiently to inhibit passage across the blood-brain barrier. The specification provides clear and adequate instructions with respect to the selection of a group that provides the mere bulk (see, for example, the specification from page 19, line 4, to page 20, line 15).

As amended, claim 12, and dependent claims 14, 15, 22-25, and 28-33, are now limited to corticosteroid conjugates in which the corticosteroid is attached to a bulky group via a linker in which these constituent components are covalently connected via an amine, amide, hydrazide, or thioether linkage (i.e., a linkage resistant to enzymatic cleavage). These linkage groups are described in the specification from page 14, line 7, to page 18, line 13, and are the linkage groups used in the Examples (see Examples 2-7). Applicants note that, as amended, claim 12 no longer recites 'a charged group of less than 400 daltons.' Finally, claim 12 is now limited to a method for treating the conditions previously listed in claim 13 (now cancelled).

Applicant asserts that the structural limitations now incorporated into claim 12 are sufficient to provide one of skill in the art a written description of the claimed method.

Applicants note that, as amended, claim 12, and dependent claims 14, 15, 22-25, and 28-33, are considerably narrowed with respect to both the recited genus of compounds and the recited indications.

In view of the amendment to claim 12 and the remarks above, Applicant requests withdrawal of the rejection for lack of written description.

Rejection under 35 U.S.C. § 102(b)

Claims 12, 13, 15, 22, 23, and 28-32 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zhang et al., *J. Pharm. Sci.* 2001 (hereafter "Zhang"). As a basis for this rejection the Office Action at pages 13, 14, and 15 states:

> ...[T]he limitations of claim 12...are inherent to the compound taught by Zhang et al. since it anticipates each and all structural limitations of the base claim. Therefore, the reference is deemed to anticipate the instant claims above.
>
> Zhang et al. teach that the conjugate is indeed resistant to in vivo cleavage, e.g., in page 2081, column 2, lines 6-12. Further, the limitation --such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion-- is not limiting, since it is only drawn to an example of the types of "resistance to in viva cleavage" that the conjugates may have.

Applicants have addressed this rejection by amending claim 12 and with the following remarks.

In maintaining this rejection the Office has, in part, relied upon page 2081, column 2, lines 6-12, of Zhang to conclude that Zhang teaches a corticosteroid conjugate that resists cleavage *in vivo*. Applicants respectfully disagree.

Zhang at page 2081, column 2, lines 6-12, describes the plasma kinetics of the DMP conjugate. The Office appears to be referring to the statement that "no unconjugated drug was detected in plasma of DMP-injected rats." However, the absence of unconjugated drug in this context is not evidence of resistance to hydrolysis. Rather, the absence of unconjugated drug is a result of altered biodistribution. The corticosteroid conjugate of Zhang is designed to be cleaved *in vivo*, releasing methyprednisolone

succinate and methyprednisolone. The purpose of the Zhang's conjugate is to target the corticosteroid to the liver and spleen. Once delivered to the targeted site, the conjugate is cleaved, releasing unconjugated corticosteroid at the site. See, for example, Zhang in the abstract, which recites:

> As for tissue distribution, the conjugate delivered the steroid primarily to the spleen and liver as indicated by 19- and 3-fold increases, respectively, in the tissue/plasma area under the curve (AUC) ratios of the steroid. On the other hand, the tissue/plasma AUC ratios of the prodrug in other organs were negligible. Active MP was released from DMP slowly in the spleen and liver, and AUCs of the regenerated MP in these tissues were 55- and 4.8-fold, respectively, higher than those after the administration of the parent drug.

Thus, the absence of unconjugated drug in the plasma compartment is a result of the fact that the DMP has distributed to the liver and spleen (i.e., the tissues where Zhang observes the cleavage of the conjugate).

As amended, claim 12, and dependent claims 14, 15, 22-25, and 28-33, are now limited to corticosteroid conjugates in which the constituent components (i.e., the corticosteroid, bulky group, and linker) are covalently connected via an amine, amide, hydrazide, or thioether linkage (i.e., a linkage resistant to enzymatic cleavage). In contrast, the prodrug of Zhang is covalently connected via two hydrolyzable ester linkages (see Scheme 1 at page 2079 of Zhang). As amended, claim 12 no longer encompasses the structural features of Zhang.

In view of the amendment to claim 12 and the remarks above, Applicant requests withdrawal of the rejection for lack of novelty.

Support for the Amendment to claim 12 and new claims 33-37

Claim 12 has been amended to include the limitation that the "(a) said corticosteroid and said linker are connected via a first linkage group, and (b) said linker and said bulky group are connected via a second linkage group, each of said first linkage group and said second linkage group selected, independently, from an amine, amide, hydrazide, or thioether linkage." Support for this limitation is found in the specification

from page 14, line 7, to page 18, line 13. Amine linkage groups are described in the specification at page 15, lines 26-28, and at page 15, lines 19-23, and at page 15, lines 16-18. Amide linkage groups are described in the specification from page 16, line 12, to page 17, line 8, and in Examples 2, 3, 6, and 7. Hydrazide linkage groups are described in the specification at page 16, lines 20-24, and in Example 4 and 5. Thioether linkage groups are described in the specification at page 15, lines 3-12.

Claim 12 has been amended to include the limitation that the "condition is selected from asthma, psoriasis, eczema, organ/tissue transplant rejection, graft vs. host reactions, Raynaud's syndrome, autoimmune thyroiditis, Grave's disease, autoimmune hemolytic anemia, autoimmune thromboeytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease, Sjogren's syndrome, urticaria, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, Crohn's disease, ulcerative colitis, lupus, tendonitis, bursitis, adult respiratory distress syndrome, shock, oxygen toxicity, glomerulonephritis, vasculitis, reactive arthritis, necrotizing enterocolitis, Goodpasture's syndrome, hypersensitivity pneumonitis, glomerulonephritis; encephalomyelitis, and meningitis." Support for this limitation is found in claim 13 as filed.

No new matter has been added with these amendments.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. To expedite prosecution applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

Enclosed is a petition to extend the period for replying for three months, to and including July 17, 2008. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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